unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6:995-1001) and Gold et al. (U.S. Patent No. 5,475,096, filed June 10, 1991).

Claims 2, 4, 5, 8-14, 17-20 and 23-45 are rejected under 35 U.S.C. §103(a) as being unpatentable over Cubicciotti (U.S. Patent No. 6,287,765, filed May 20, 1998) in view of Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-5299) and Gibson et al. (Genome Methods 1996, 6:995-1001).

Applicants invention, as now claimed, provides a method for quantitating or detecting the presence of a target molecule in a sample which may contain the target molecule and a nuclease, and includes the step of washing the antibody:target molecule:aptamer ternary complex to remove the nuclease. As shown in the specification at page 36, lines 11-23 and as supported at page 31, line 20 and page 32, lines 7-11 of the specification, Applicants discovered that aptamers could be effectively employed in the method of the invention when nucleases are present. This discovery was completely contrary to the understanding in the relevant art at the time of the invention. In fact, a reference cited by the Examiner, at Column 24, lines 51-53 reflects this general understanding that teaches away from the successful use of aptamers if nucleases are present in the sample. Gold et al. states, "This process must be done without chemical degradation of the selected nucleic acids and must result in amplifiable nucleic acids." The presence of nucleases in the sample would understandably not be acceptable to the teaching of Gold et al. Further, Williams et al., Proc. Natl. Acad. Sci. USA, Vol. 94, pp 11285-11290, October 1997 evidences the general understanding at the time of the present invention that "The utility of aptamers is often limited by their vulnerability to nucleases present in biological materials." (Williams et al. at 11285, Abstract.

Also see Williams et al. at the following first full paragraph p. 11285). A copy of Williams et al. is provided as an attachment for the convenience of the Examiner.

Thus, the understanding of one of ordinary skill in the art, as evidenced by the references cited above, would be that the method of the present invention would not be effective. This teaching away from the Applicants invention, as now claimed, is not overcome by any teaching or suggestion of the other art of record.

Applicants therefore respectfully suggest that the invention as now claimed is patentable over the prior art, which is relied upon in both rejections recited above. Accordingly, withdrawal of the current rejections under 35 U.S.C. §103(a) is requested.

## CONCLUSION

In light of the above, Applicants believe that this application is now in condition for allowance and therefore requests favorable consideration.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below prior to entering an subsequent Official Action in this matter.

Respectfully submitted,

PIPER RUDNICK LLP

Dec 9, 2002

Date

Steven B. Kelber
Registration No. 30,073
Attorney of Record

Perry E. Van Over
Registration No. 42,197

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085

SERIAL NO. 09/449,204

DOCKET NO.: 9491-047-27

**MARKED-UP COPY OF AMENDED CLAIMS**

2. (Twice Amended) The method of Claim 46 [23], further comprising washing the capture antibody:target molecule complex to remove unbound sample after step (a).

4. (Twice Amended) The method of Claim 46 [23], wherein the capture antibody is bound to a solid support or carrier during step (a) or (b).

5. (Twice Amended) The method of Claim 46 [23], wherein the capture antibody is in solution during step (a) or (b).

8. (Twice Amended) The method of Claim 46 [23], wherein the target molecule is an organic compound having a molecular weight of about 100 to about 1000 grams/mole.

9. (Twice Amended) The method of Claim 46 [23], wherein the target molecule is a protein or fragment thereof.

11. (Twice Amended) The method of Claim 46 [23], wherein the sample is selected from the group consisting of blood, serum, sputum, urine, semen, cerebrospinal fluid, bronchial aspirate and organ tissue.

13. (Twice Amended) The method of Claim 46 [23], wherein the detectable non-primer probe comprises a nucleic acid having a fluorescent dye label.

17. (Thrice Amended) The method of Claim 46 [23], wherein the nucleic acid detector molecule is RNA and the RNA detector molecule is reverse transcribed to form DNA before or during amplifying step d [)].

18. (Twice Amended) The method of Claim 46 [17], wherein the RNA detector

molecule is reversed transcribed at a temperature sufficient to dissociate the detector molecule from the capture antibody:target molecule:aptamer ternary complex and reverse transcribe the RNA.

24. (Amended) The method of Claim 46 [23], wherein said quantitating or detecting the PCR amplified DNA quantitates or detects the target molecule when present at a concentration equal to or less than about 1000 pg/mL.

27. (Amended) The method of Claim 46 [23], wherein said quantitating or detecting the PCR amplified DNA quantitates or detects the target molecule when present at a concentration of about 100 to about 5000 pg/mL.

30. (Amended) The method of Claim 46 [23], wherein said quantitating or detecting the PCR amplified DNA quantitates or detects the target molecule when present at a concentration of about 3 to about 5000 pg/mL.

33. (Amended) The method of Claim 46 [23], wherein said quantitating or detecting the PCR amplified DNA quantitates or detects the target molecule when present at a concentration of about 0.4 to about 5000 pg/mL.

36. (Amended) The method of Claim 46 [23], wherein said quantitating or detecting the PCR amplified DNA quantitates or detects the target molecule when present at a concentration of about 1 to about 5000 pg/mL.

39. (Amended) The method of Claim 46 [23], wherein said quantitating or detecting the PCR amplified DNA quantitates or detects the target molecule when present at a concentration of about 0.03 to about 5000 pg/mL.

42. (Amended) The method of Claim 46 [23], wherein said quantitating or detecting the PCR amplified DNA quantitates or detects the target molecule when present at a concentration of about 0.005 to about 5000 pg/mL.